LNCT GROUP OF COLLEGES

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Subject: Pharmacology-III (BP 602T)
Unit: IV
Topic: Chemotherapy Of Malignancy

➢ Contents :

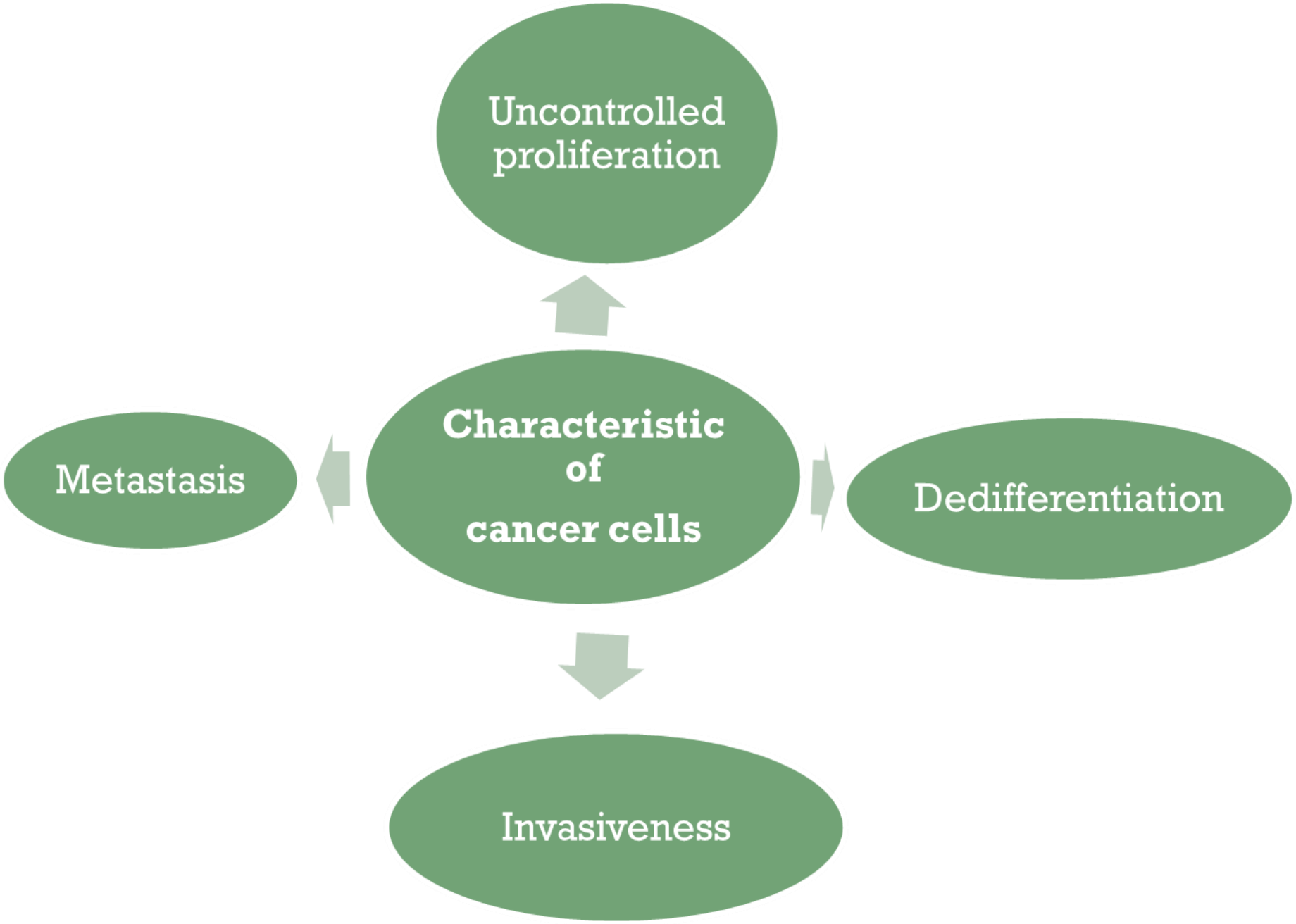
- Introduction
- Types of cancer
- Aetiology of cancer
- Pathogenesis of cancer
- Diagnosis of cancer
- Treatment of cancer
- Novel drugs for cancer
- Future prospects
- Reference

➢ Introduction :

- Also known as **Neoplasm** / **Tumor**.
- **Define** :

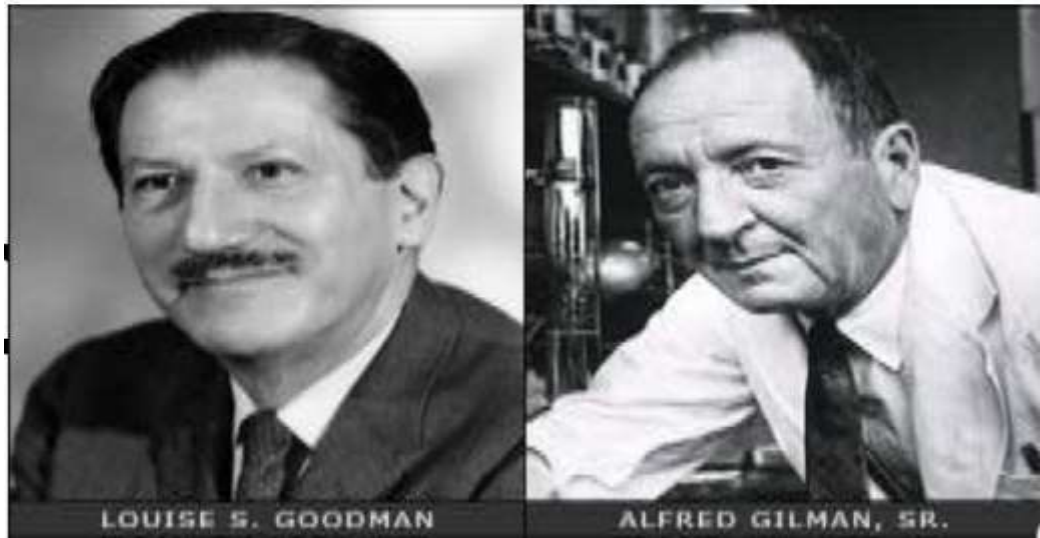
The term cancer refers to a disease of cells that show uncontrolled proliferation, dedifferentiation, invasiveness and the ability to metastasise.

- When such cells proliferate excessively, they form local tumors.
- The extent of metastasis and deterioration in metabolic processes resulting from cancer leads to eventual death of the patient.


Uncontrolled proliferation
Characteristic of cancer cells
Metastasis
Dedifferentiation
Invasiveness

The origin of cancer chemotherapy.....

- **WW (I)** exposure to **mustard gas** led to the observation that **alkylating agents** caused BMD and lymphoid hypoplasia which was further studied during **WW(II)**.
- This observation led to the direct application of such agents to patients with Hodgkin's disease and lymphocytic lymphomas at Yale Cancer Centre in 1943, **Luis Goodman** and Alfred **Gillman** demonstrated it for the first time.



- 1948, Sydney Farber successfully used **Antifolates** to induce remission in children with all.

- 1955, National chemotherapy program begins at National cancer institute, a systematic programme for **drug screening**.

- 1958, Roy Hertz and Min Chiu Li demonstrated **Methotrexate** as a single best agent for choriocarcinoma, the first solid tumour that can be cured by chemotherapy.

- 1959, **FDA** approved the **alkylating agent**, **Cyclophosphamide**
- 1965, The era of **combination chemotherapy begins**.

➢ Types of cancer :

Benign tumors	Malignant cancers
Slow growing	Rapidly proliferate
Resemble normal cells	Manifest dedifferentiation, invasiveness
Remain localised	Ability to metastasise
Usually not harmful	Damage to the surrounding cells and are harmful if left untreated.

Tumors are categorized according to their tissues of origin:

- **1) Benign tumors:** name usually end with “oma”

Type of tumor	Origin tissue
Pailloma	Surface epithelium
Adenoma	Glandular epithelium
Melanoma	Pigment cells
Myoma	Muscle tissue
Fibroma	Fibrous tissue
Neurofibroma	Nerve sheath.

2) Malignant cancer:

– Solid tumors
– Hematological malignancie

a) Solid tumors are of the following types:

Type of tumors	Origin tissue
Carcinomas	Surface epithelial tissue
Adenocarcinomas	Glandular epithelial tissue
Sarcomas	Connective tissue
Neurofibrosarcoma	Nerve sheath
Myeloma	Haemopoietic tissue of bone marrow

b) Haematological malignancies :

- Lymphomas
- Leukaemia

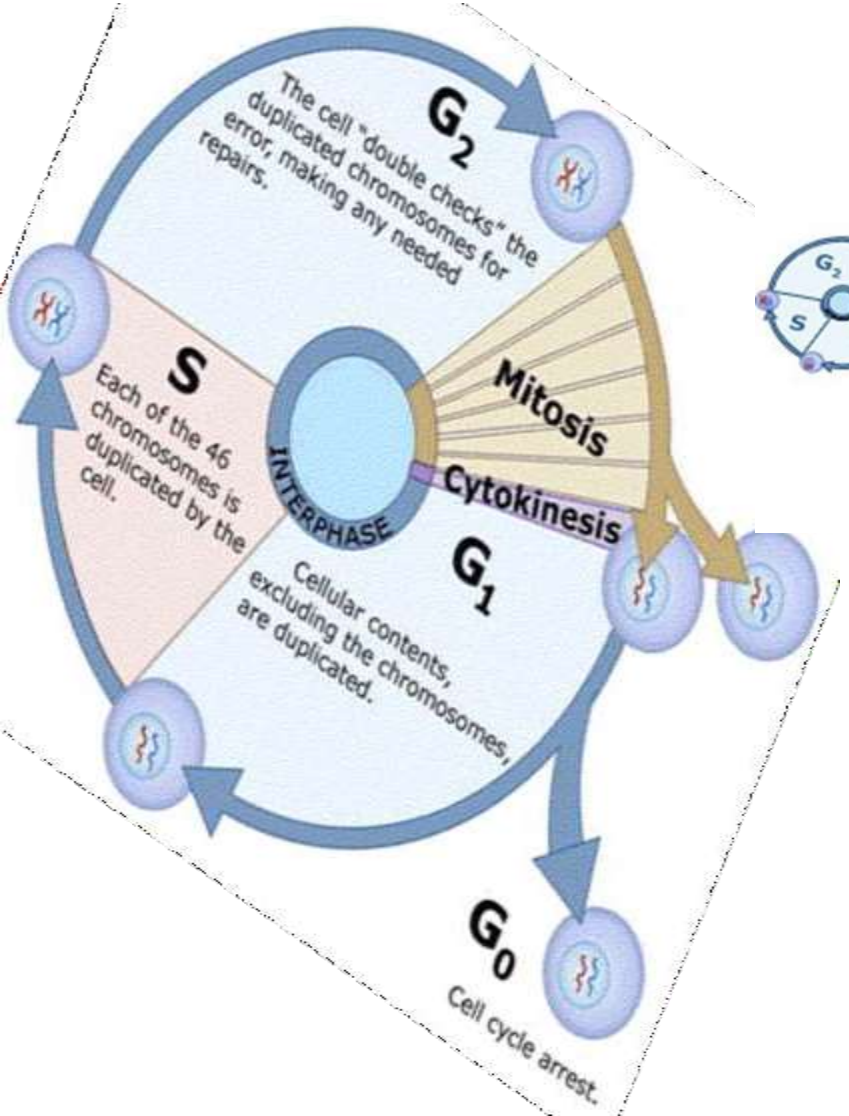
- **Lymphomas**:- tumors of lymphatic system

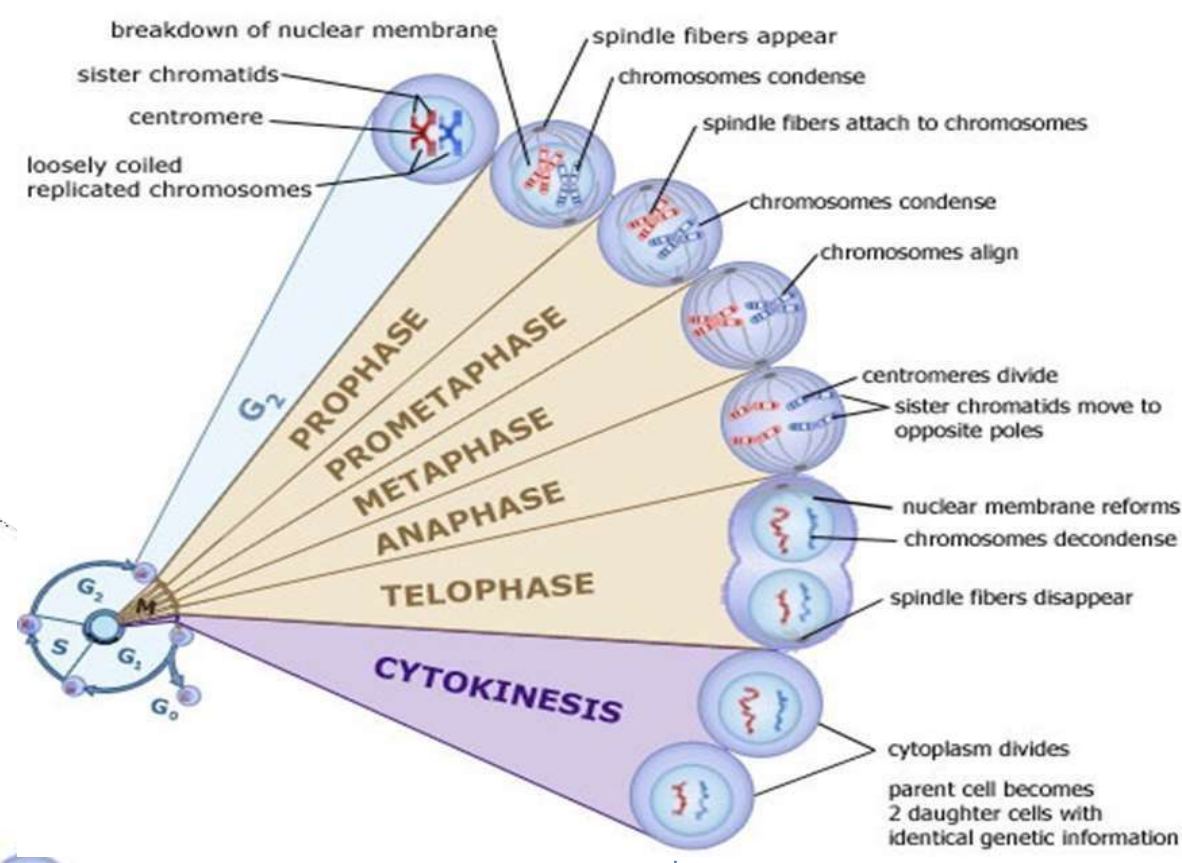
Type of lymphoma	Origin tissue
Hodgkin's lymphoma	B-cell origin involving lymph nodes
Non-Hodgkin's lymphoma	Extra nodal involvement including blood and bone marrow
T-cell lymphoma	T-cell

- **Leukaemia** : is a type of **blood cancer** resulting due to disorganised proliferation of abnormal leukocytes.

Type of leukaemia	Tissue origin
Acute leukaemia	Overproduction of immature cells which prevent the normal production of RBCs and platelets.
Acute lymphoid/lymphoblastic leukaemia	The neoplastic proliferation affects lymphoid cells lines with lymphocytosis.
Acute myeloid/myelogenous/non-lymphblastic leukaemia	The neoplastic proliferation affects myeloid cell lines (mainly haematopoietic tissues involving granulocytes from myeloblasts).
Chronic leukaemia	Accumulation of mature leukocytes in the peripheral blood stream.
Chronic lymphocytic/lymphoid leukaemia	The neoplastic proliferation affects lymphoid cells lines.
Chronic myeloid/ granulocytes leukaemia	The neoplastic proliferation affects myeloid cell lines.
Hairy cell leukaemia	B-cell lymphoproliferative disorder characterised by the blood cells with cytoplasmic villi.

Cell cycle regulation :



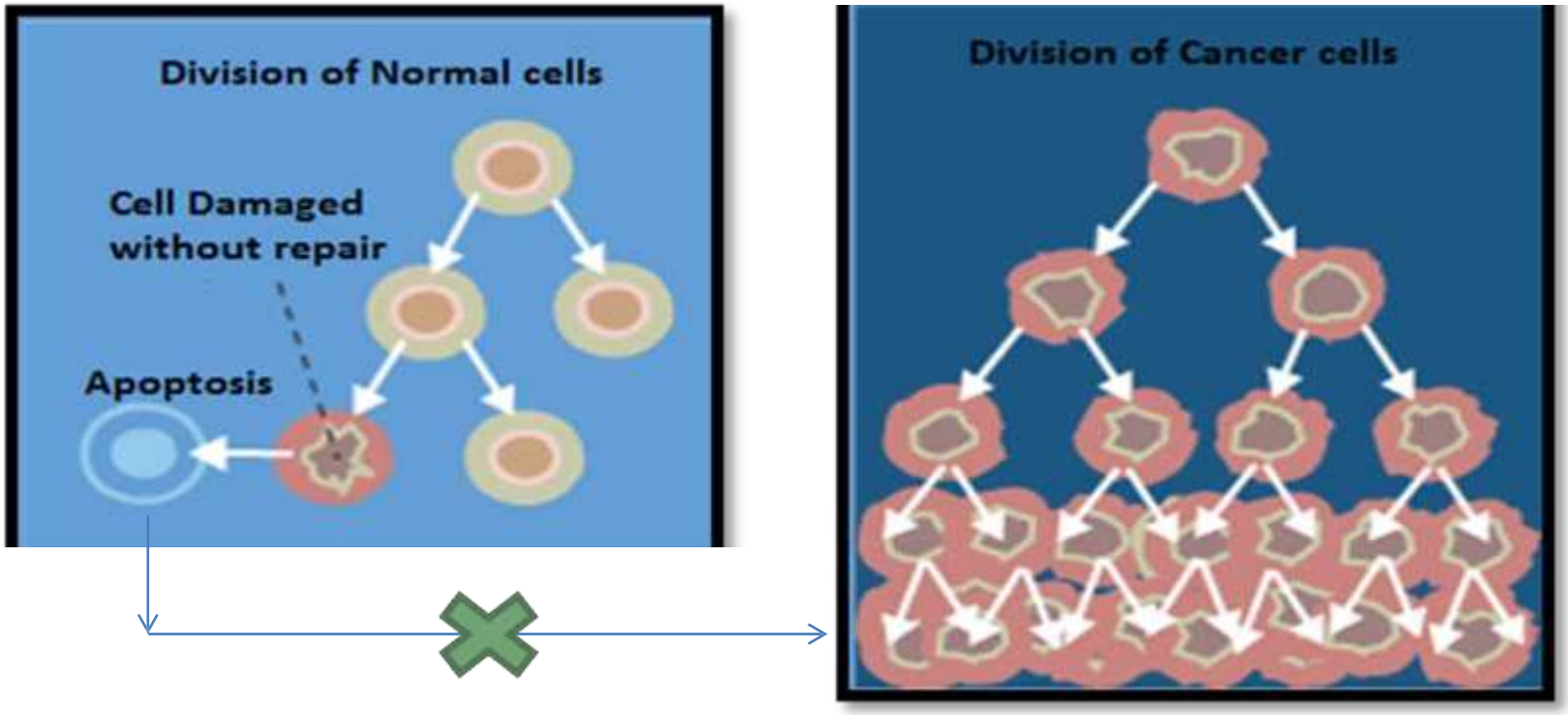


- If no regulation take place,

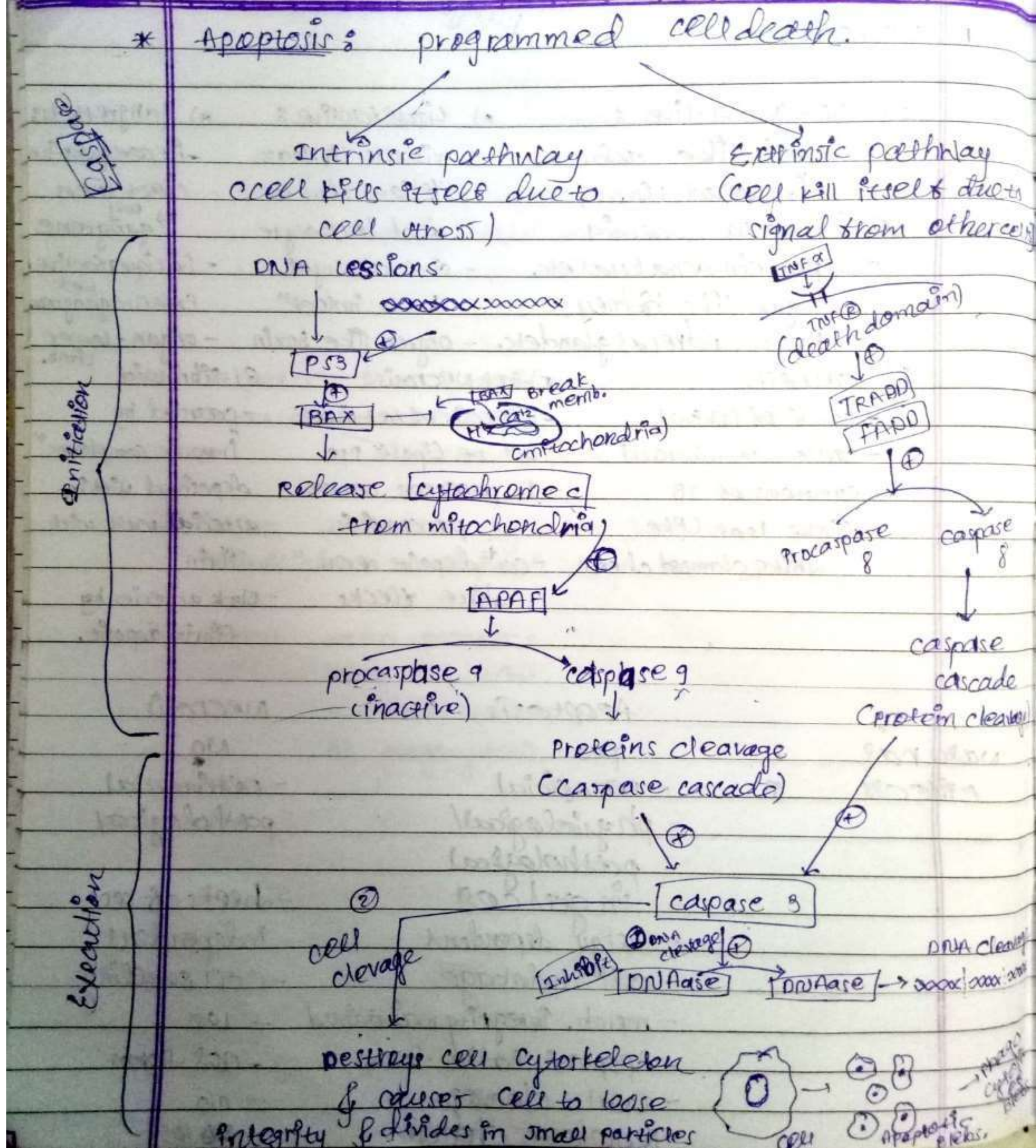
Abnormal cell formation may occure

Leads to cancer

- ***Apoptosis*** : development of resistance to apoptosis is a hallmark of cancer.



Apoptosis :



Apoptosis : programmed cell death.
Caspase
Intrinsic pathway
(cell kills itself due to cell stress)
DNA lessions
P53
BAX
BAX break memb.
mitochondria
Release cytochrome c from mitochondria
APAF
procaspase 9 (inactive)
caspase 9
Proteins cleavage (Caspase cascade)
Initiation
Extrinsic pathway
(cell kill itself due to signal from other cells)
TNF α
TNF R
(death domain)
TRADD
FADD
Procaspase 8
caspase 8
caspase cascade
(Protein cleavage)
Execution
caspase 3
cell clevage
DNA cleavage
Inhibit
DNAase
DNA cleavage
Destroys cell cytoskeleton & causes cell to loose integrity & divides in small particles
cell
Apoptotic bodies

➢ Aetiology of Cancer :

- ***Carcinogenic chemicals :*** *Having ability to react with DNA and induce neoplasm.*
  - ***INITIATOR -*** *the agent which* ***directly*** *or after metabolic alteration interact with DNA to produce tumer growth.*
  - ***PROMOTOR –*** *The agent which by it* ***self cannot induce*** *tumor but promote tumor by bringing about an alteration in endocrine function or unmasking the effect of virus or genotoxic initiator.*

- ***Environmental and occupational hazards*** such as exposure to ionizing and UV **radiation** and exposure to variable **chemical** carcinogens like azo dyes, arsenic, vinyl chloride, asbestos, benzene and PVP.

- ***Viruses*** such as Epstein-barr virus, hepatitis-b virus and human papilloma virus etc.

- ***Diet and habits*** such as high fat and low fiber diet, tobacco, smoking and alcohol consumption.

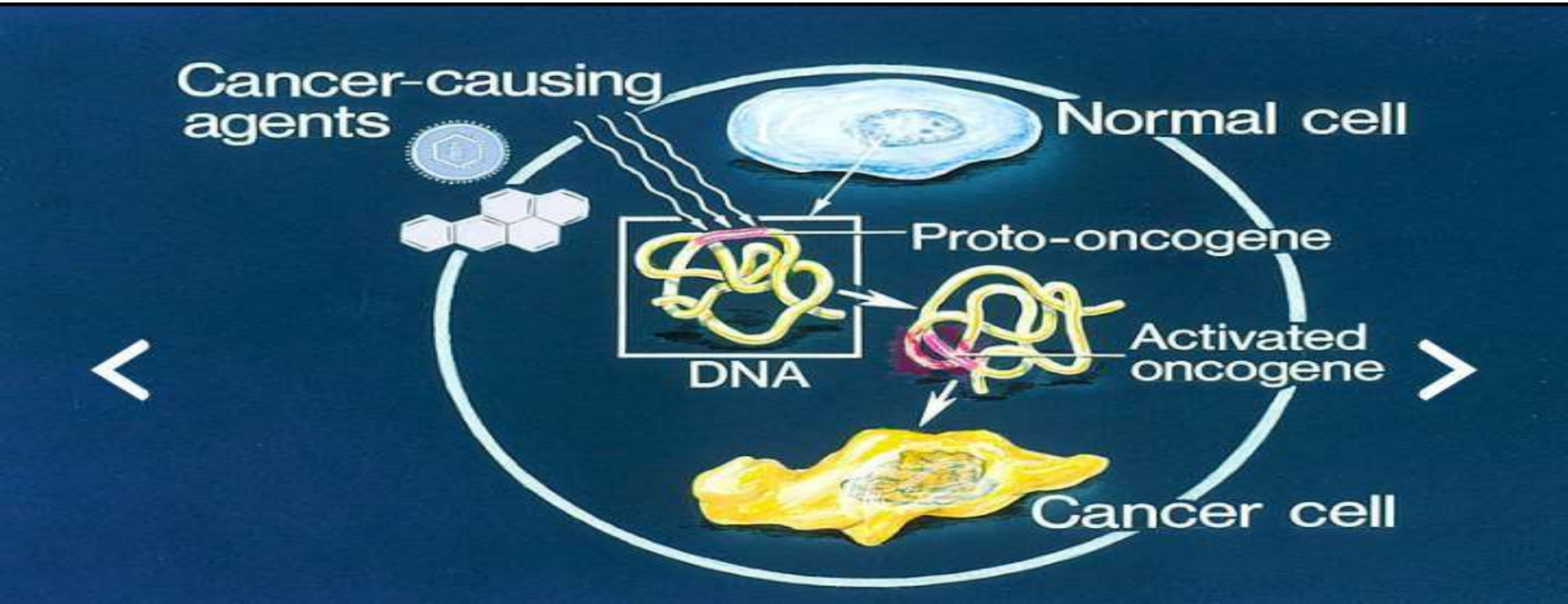
- ***Genetic factors*** such as inherited genetic mutation expression of oncogenes and repression of tumor suppressor genes.

- ***Use of drugs*** like immunosuppressant.

➢ Pathogenesis of a cancer cell :

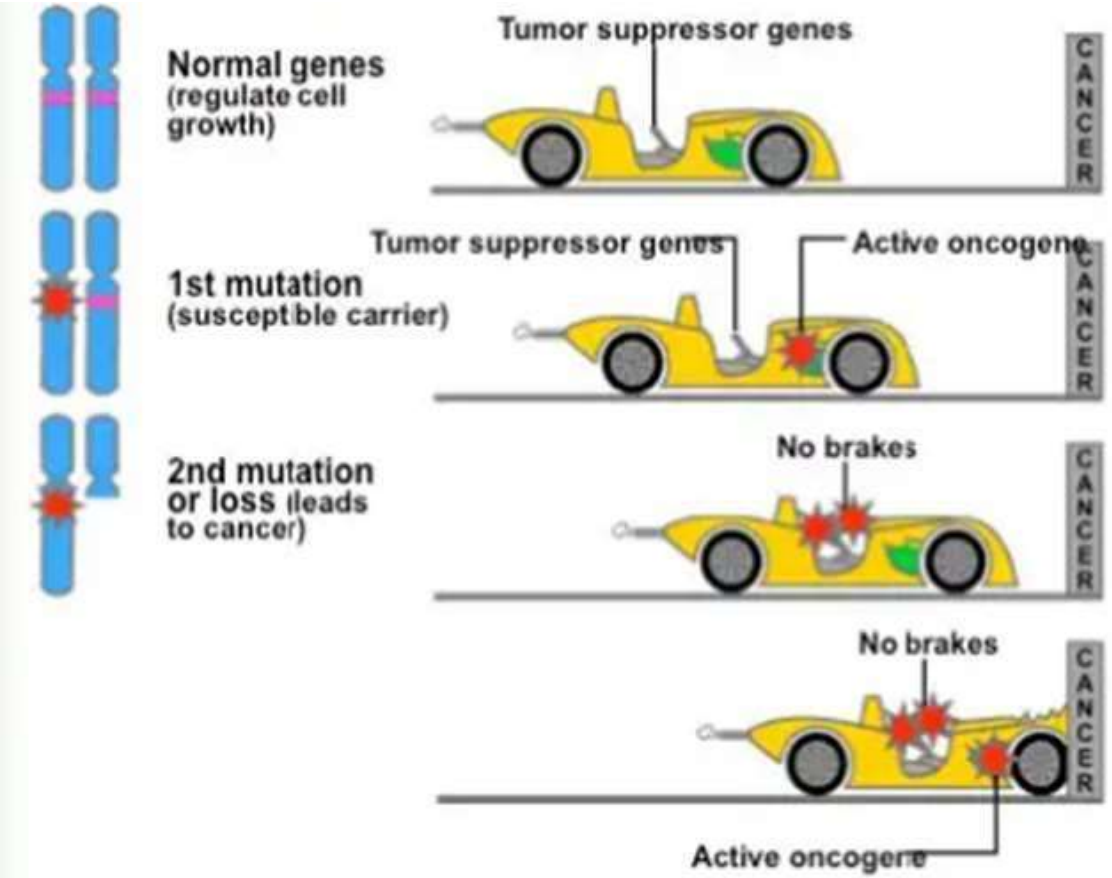
❑ Activation of proto-oncogenes to oncogenes:

Proto-oncogenesis are genes that normally control cell division, apoptosis and differentiation but which can be converted to oncogenes by viral or carcinogenes action.



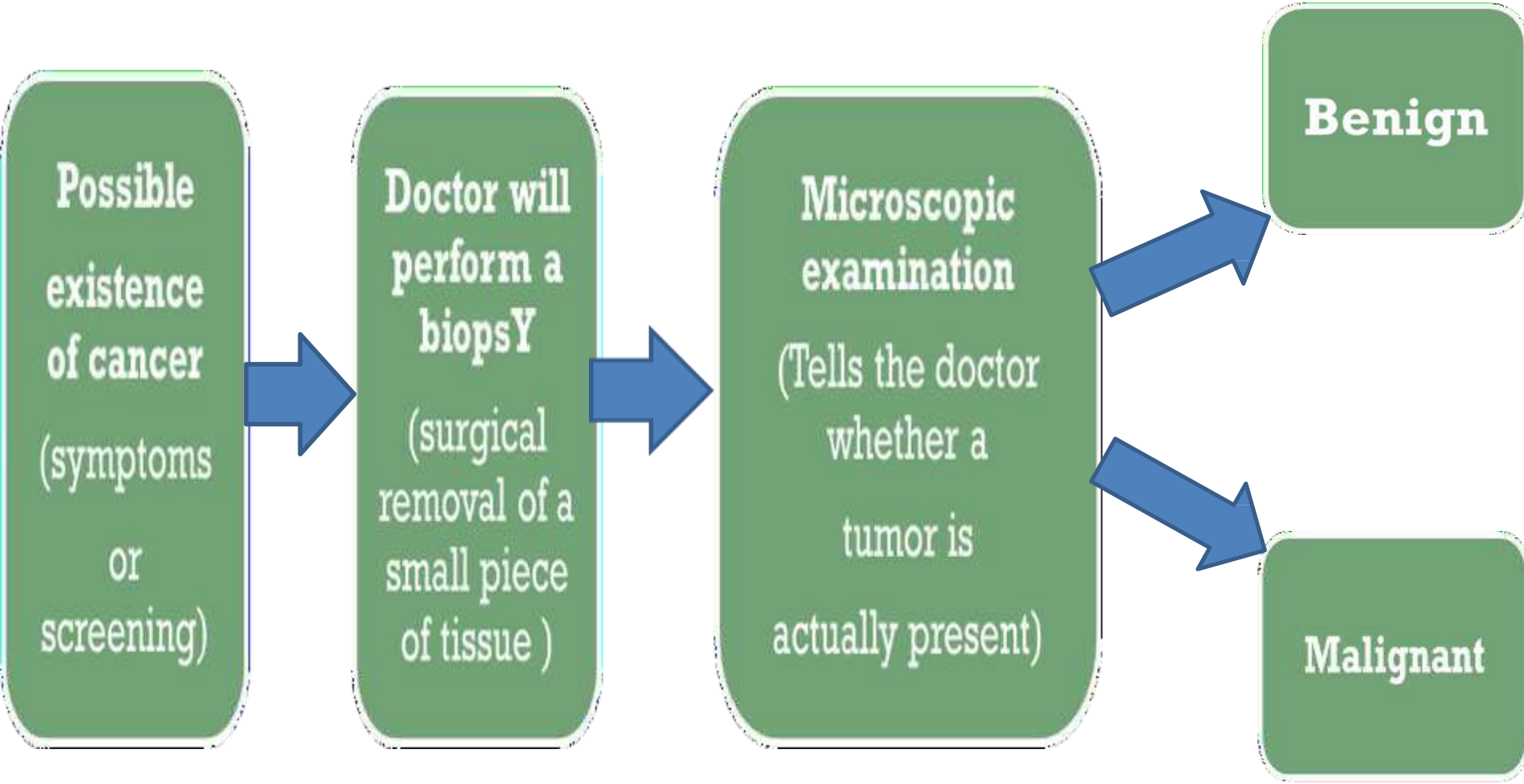
❑ Inactivation of tumor suppressor genes:

Normal cells contain tumor suppressor genes that have the ability to suppress malignant change. The loss of function of tumor suppressor genes can be the critical event in carcinogenesis.



Tumor suppressorgenes are normal genes whose **ABSENCE** can lead to cancer.

➢ Diagnosis of the Cancer :



Diagnosis with tumor markers :

Marker	Cancer
Carcinoembryonic antigen (CEA)	Colon carcinoma
α-Fetoprotein	Hepatoma
β Subunit of human chorionic gonadotropin (β-hCG)	Gestational trophoblastic neoplasia (GTN)
Prostate-specific antigen (PSA),	Prostatic carcinoma
β2-Microglobulin	Myeloma and lymphoma
CA 125	Ovarian cancer
Chromogranin A	Carcinoid and neuroendocrine cancer
Thyroglobulin	Thyroid cancer
CA 15 and CA 27	Breast cancer
CA 19	Pancreatic cancer

Diagnosis :

- **Endoscopy** i.e. bronchoscopy, cystoscopy
- **Radiology**

  Computed tomography(CT scanning)

  Magnetic resonance imaging (MRI)
- **Biopsy**
  - Needle Biopsy
  - Surgical Biopsy

Stages of cancer :

- **Four** types of stages; stage1, stage 2, stage 3, stage 4.
- Staging tells us the extent of the disease.
- Treatment depends on the stage of the specific cancer.
- Staging helps determine the patient's prognosis (prediction of course and outcome of disease, especially chances of recovery)

➢ Treatment of Cancer :

1. Chemotherapy
2. Surgical resection
3. Radiotherapy
4. Immunotherapy

- **Chemotherapy** :-

- Cancer cells are more sensitive to **antineoplastic drugs** when the cells are in the process of growing and dividing.
- Chemotherapeutic drug having many **side effect** ….
  - BMD
  - Loss of hair
  - Nausea & vomiting
  - Increase susceptibility to infection
  - Teratogenicity in pregnant women

Classification of the anticancer agents:

- Cell cycle specific agents

Go phase – Alkylating agent

G1 phase – Asparaginase & steroids

S phase –antimetabolite,camptothecin, cisplatin,doxorubicin,hydroxyurea

G2 phase- Bleomycin,epipodophylotoxin

M phase – taxans &Vinca alkaloids

➢ Alkylating agents :

A) Nitrogen mustards :

chlorambucil,cyclophosphamide,mechlorethamine HCl, uracil mustard, Ifosfamide

B) Ethylenimines:

thiotepa, hexamethylmelamine,triethylenemelamine

C) Nitrosoureas :

carmustine, lomustine, semustine, streptozotocin

D) Alkylsulfonates : **busulphan**

E) Thiazenes : **decarbazine**

F)Platinium based alkylating agent : **cisplatine**, carboplatin, oxaliplatin

G) Methylhydrazines : **Procarbazine**

- **Antimetabolites** :
  - Folic acid antagonist : methotrexate (Mtx)
  - Pyrimidin analogues : 5- FU, cytarabine, azarabine, floxuridine
  - Purine analogues : 6-MP, 6- TG, azathioprine, fludarabine

- **Natural products** :
  - Vinca alkaloids : vincristine, vinblastine
  - Epipodophylotoxin : etoposide, teniposide
  - Taxane deri. : paclitaxel, docelatel
  - Campothesins deri.: irinotecan, topotecan

- **Antibiotics** : actinomycin- D, daunorubicin,doxorubicicn, mitomycin, bleomycin
- **Enzymes** : L- Asparaginase

- **Monoclonal antibody** : Rituximab, Trastuzumab

➢ Hormonal drugs :

- Glucocorticoids – Prednisolone and others
- Estrogen – Fosfestrol, Ethinylestradiol
- Selective estrogen receptor modulators - Tamoxifen ,Toremifene
- Selective estrogen receptor down regulators – Fulvestrant
- Aromatase Inhibitors – Letrozole, Anastrozole , Exemestane
- Anti androgens – Flutamide,Bicalutamide
- 5-α reductase Inhibitors – Finasteride, Dutasteride
- GnRH analogues – Nafarelin,Leuprorelin,triptorelin
- GnRH antagonists – Cetorelix, Ganirelix, Abarelix
- Progestins – Hydroxyprogesterone acetate, etc.

Alkylating agents

- MOA :

-this are compound that are capable to **introduce alkyl group** into N site Of **DNA , RNA** or any enzyme through **covalent bond** or may cause….

a) Miscoding
b) Destuction of guanine
c) Distruption of nucleic acid function

-act on 7 position of **G-base** in each double stranded DNA to give 7- **alkyl guanine** & causing cross linking that interfere with seperation of strand & prevent mitosis.

- the effect of base alkylation include misreading of DNA codon & single strand breakage of DNA chain. Long time effect may cause mutation & cell death.

-Most favoured site on DNA is N-7 POSITION OF A,G,C & even sugar phosphate group.

- Nitrogen mustards & ethyleneimines act by above mech.
- Busulfan act by ‘sulfur stripping’.
- Nitrosoureas act through liberation of alkylation moiety. (stz produce S.E. on pancreas.)

A) Nitrogen mustards :

cyclophosphamide, **chlorambucil**, **mechlorethamine HCl**, uracil mustard, Ifosfamide

- This are cytotoxic chemotherapeutic agent similar to mustard gas.

a) Cyclophosphamide :

- Inactive invitro but when it administered ,it is **metabolized** by liver into **phosphoramide** & **acrolein**. (active comp.)
- Phosphoramide : cytotoxic to cancer cell
- Acrolein : toxic to bladder
- Not propely absorb by oral route so better to be given by **I.V.**
- **USED** :in treat to lymphosarcoma,breast,ovarian,lung cancer
- **A.E**. : N/V/D, BMD, darkening of skin/nails , pulmonary fibrosis, UTI
- **Dose** – 2-3 mg/kg/day oral , 10-15 mg/kg i.v every 7- 10 days

b) mechlorethamine HCl :

- Taken by **I.V. infusion**
- **Used** to treat prostate cancer
- **A.E**. : allergic reaction, thrombophlebitis, herpes zooster infection,mutagenic & carcinogenic effect on bone marrow stem cell.
- **Dose**- 0.1 mg/kg iv daily x 4 days ; courses may be repeated at suitable intervals

c) Chlorambucil :

– Slow acting alkylating agent, esp. active against lymphoid tissues, myeloid tissues – largely spared (Ch. Lymphatic leukaemia and non-Hodgkin's lymphoma)

-**Dose** – **orally** 0.1-0.2 mg/kg daily for 3-6 weeks, then 2 mg daily for maintenance

- **A.E.** : muscle problem, numbness of hands/feet, hepatotoxicity

B) Nitrosoureas :

carmustine, lomustine, semustine, streptozotocin

- 2 functional group : Nitroso + Urea
- highly lipid soluble, & having ability to **cross BBB** (So used in brain tumor, meningeal leukaemia) **(i.v.)**
- **A.E.** : pulmonary toxicity, nephrotoxicity, N,V - common , CNS effects BMD –delayed -6 weeks , Visceral fibrosis and Renal damage

C) Alkylsulfonates : busulphan**(i.v.)**

- alkyl sulfonate ,
- highly selective for myeloid elements; Granulocyte precursors(most sensitve) > Platelets and RBC
- **USED** : to treat chronic myelogenous leukaemia (CML) in bone marrow transplantation patients.
- **A.E.** :N/V/D, Constipation, Seizure, little effect on lymphoid tissue and GIT Hyperuricemia(common); Pulmonary fibrosis and skin pigmentation – specific adverse effect

D) Ethylenimines: Thio-TEPA **(i.v)**

- High Toxicity
- **USED** – Ovarian and Bladder Cancer

E) Thiazenes : decarbazine **(i.v.)**

- after activation in liver – methylating DNA ,
- most imp. Indication – malignant melanoma, also – Hodgkin's lymphoma

F) Methylhydrazines : **Procarbazine(i.v./orally(gel capsule))**

- In vivo they convert into azo der. Or active against tumor cells.
- **Used :** in Hodgkin's disease with combination of MVPP.

M – mechlorethamine
V - vincristine
P - Procarbazine
P - prednisone

G) Platinium based alkylating agent :

cisplatine, carboplatin, oxaliplatin

- They having no alkyl group , but also damage DNA, & trigger apoptosis.
- platin is only heavy metal comp. used in cancer.

a) Cisplatine :

- Act against cells which in S- phase, M-phase,
- Effects resemble – alkylating agent and radiation
- Plasma protein bound, penetrates tissues ,Slowly excreted in urine,
- T1/2 – 72 hrs
- **Used** : ovarian, testicular, endometrial , bladder ,Lung and Oesphageal Cancer
- **A.E**. : N,V,(ondensetron) Aloplacia,maylosuppression,nephrotoxicity , Ototoxicity, Electrolyte disturbances : Hypokalemia, Hypocalcemia and Hypomagnesemia ,Rarely Anaphylactic shock , Mutagenic , Teratogenic and Carcinogenic properties,
- **Dose** – Cisplatin adm. Slow **i.v infusion** 50-100 mg/m2 BSA every 3-4 weeks

Antimetabolites :

- They are structurally related to normal compounds that present with in cell.

- They generally interfere with…

a) availability of purine or pyrimidine nucleotide precursors.

b) Either by inhibiting their synthesis

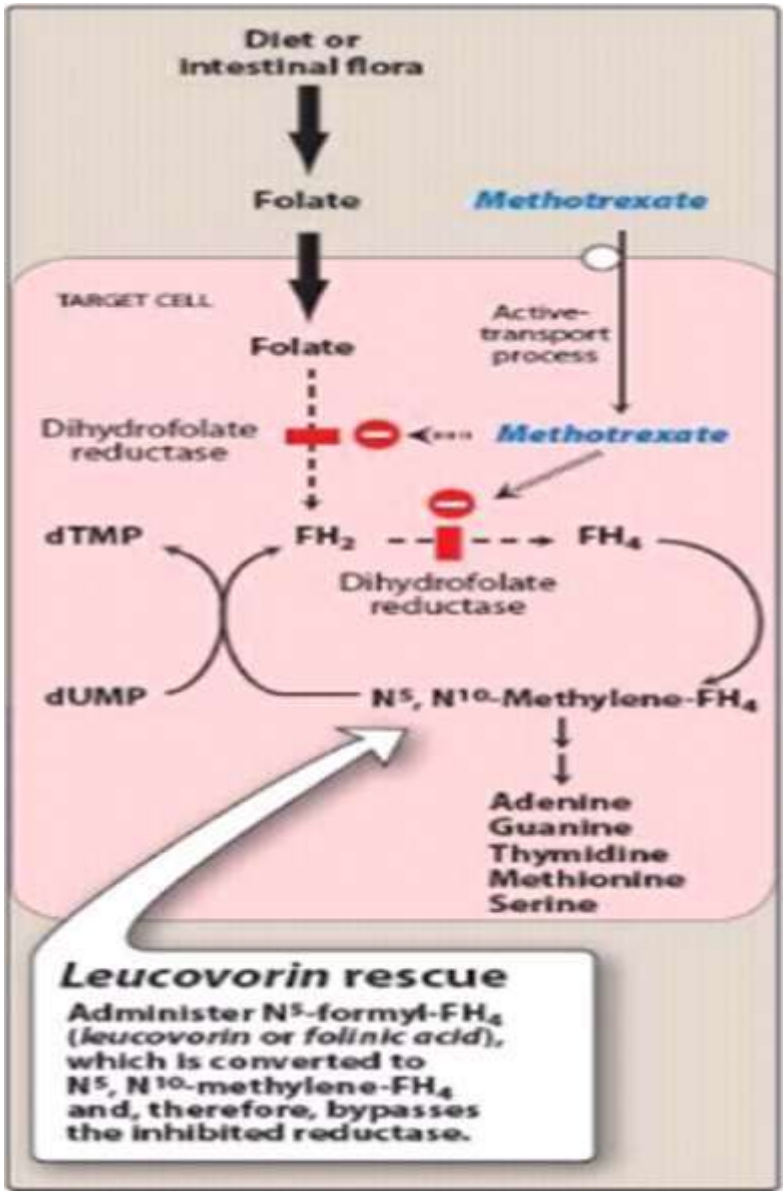
c) or by competing with them in DNA or RNA synthesis.

- Their max. cytotoxic effect are in S –phase (there for, cell cycle specific)

A) Folic acid antagonist : methotrexate (Mtx)

➢ MOA :

- Folic acid is an essential dietary factor.
- It is converted by enzymatic reduction to a series of tetrahydrofolate cofactors that provide carbon groups for synthesis of precursors of DNA & RNA.
- Mtx **inhibits** the enzyme **DHFR**. Which leads to depletion of tetrahydrofolate cofactor used for DNA & RNA synthesis.
- Also used to **inhibite** thymidylate synthase **(TS)**



- In inhibition of DHFR can only be reversed by a thousand fold excess of the natural sub. ,DHF , by adm. Of leucovorin.
- Folinic acid, thymidine also counteracts Mtx toxicity.
- **Dose** – choriocarcinoma; 15-30 mg/day for 5 days orally or 20-40 mg/m2 BSA **i.m.** or **i.v.** twice weekly,
- Low dose Mtx (7.5-30 mg once weekly) – Rheumatoid Arthritis, psoriasis,

➢ RESISTANCE :

- Reduction of affinity of DHFR to MTX
- Diminished entry of MTX into cancer cells
- Over production of DHFR enzyme

➢ USES :

- combine with other drug in..
- Lymphocytic leukaemia, breast cancer, head & neck carcinoma
- In low dose effective against some inflammatory disease, like….
- severe psoriasis , rheumatoid arthritis, crohn disease , etc..
- Other Uses – Psoriasis, IBD and in Organ transplantation

- **PK :**

- Routes of Adm. : oral, I.M., I.V., I.T.
- 50% bound to plasma proteins, Poorly crosses BBB
- Metabolism : Mtx to polyglutamate deri., or at high dose undergo hydroxylation at 7 position & form 7- OHMtx.
- Less water soluble, so produce crystalluria.
- Excreted by urine.

- **A.E. :**

- stomatitis, rash, urticaria, alopecia, myelosuppression,
- Most frequent toxicities : n/v/d
- Hepatic function : long term use of Mtx may lead to cirrhosis
- Renal function : variable
- Neurological toxicities : meningeal irritation, stiff neck, fever, headache, rarely seizures

- **C.I. :**

- because Mtx is teratogenic in exp. Animals & is an abortifacient, it should be avoided in pregnancy

B) Purine analogues :

6-MP, 6- TG, azathioprine, fludarabine

- Highly effective agent
- Purine antagonist used for treatment of malignant tumer (6-MP, 6-TG)but also prove beneficial for treating neoplastic disease (immunosuppresion (azathioprine) and in antiviral chemotherapy (acyclovir, ganciclovir, vidarabine, zidovudine))

➢ 6-MP :

- **MOA** :
- 6-MP **inhibit** the **conversion of inosine monophosphate to adenine & guanine** nucleotide formation, which are responsible for RNA & DNA formation.

- **Nucleotide formation** : 6-MP converted to the nucleotide analog,6-MP-ribose phosphate (6- thioinosinic acid, or TIMP)
- **Inhibition of purine synthesis** :TIMP can inhibite the first step of De novo purine ring biosynthesis.
- **Incorporation into nucleic acids** :TIMP converted to thioguanine monophosphate (TGMP)which after phosphorylation to di.& triphosphates can be incorporated into RNA. The deoxy-ribonucleotide analogs are also formed are incorporated into DNA. This results in nonfunctional RNA & DNA.

- **PK** :

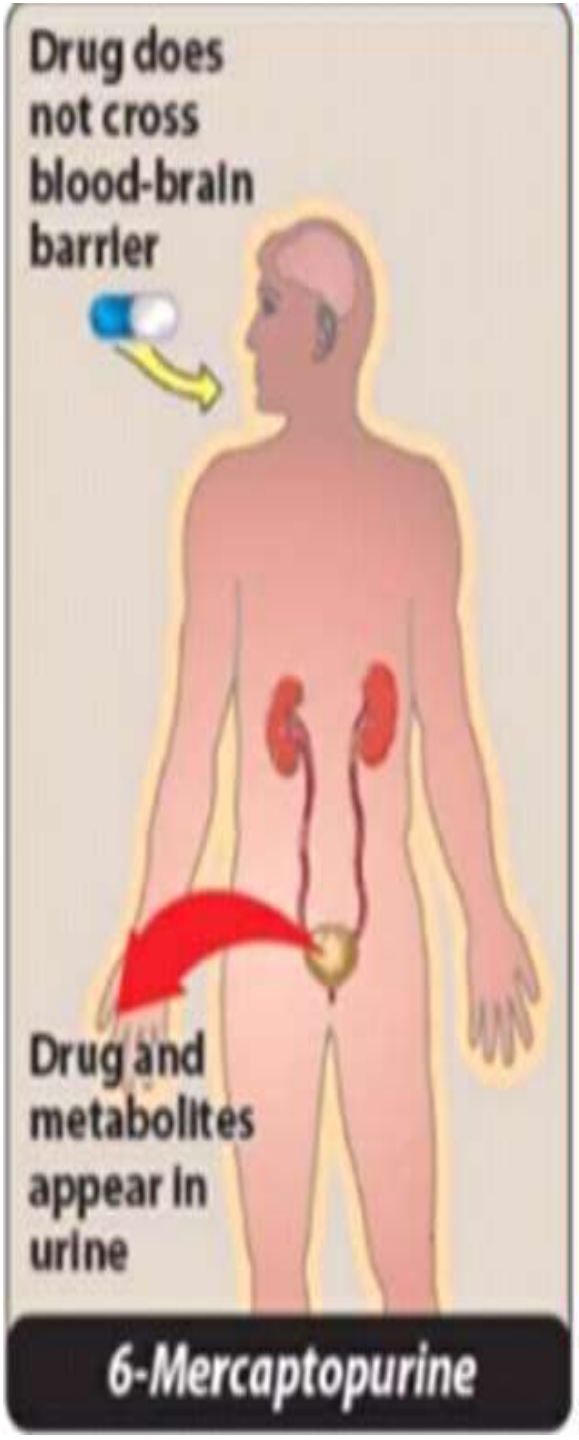
- Oral administration,well distributed except for the CSF.
- Metabolized in the liver, 6-MP is converted into 6- ethylMP deri. Or to thiouric acid.
- The parent drug & its metabolites are excreted by kideny.

- **AE** :

-BMD (major),anorexia, n/v/d

-hepatotoxicity in the form of jaundice has been reported in about one third of adult patients.

- **Dose** : 2.5 mg/kg/day, half dose for maintenance



6- TG

- 6-TG is also purine analog,is primarily used in treatment of acute nonlymphocytic leukemia in combination with Daunorubicin & cytarabine.

➢ **MOA** :

- **Converted 6-TG/6-MP** to **TGMP** by **enzyme** hypoxanthineguanine phosphoribosyltransferase **(HGPRT)**
- TGMP further converted into di. & tri. phosphate
- Which inhibite biosynthesis of GMP to guanosine diphosphate

➢ **PK** :similar to 6- MP

➢ **AE** :

- BMD

-TG is not recommended for maintenance therapy or continuous long term treatment due to the risk of liver toxicity.

- **Dose** : 100-200 mg/m2 /day for 5-20 days

C) Pyrimidine analogues :

5- FU, cytarabine, azarabine, floxuridine

➢ MOA :

- **5-FU** converted into 5-fluro-2-deoxyuredinemonophosphate **(5-FduMP)** which **inhibite thymidylate synthase** and **blocks** the **conversion** of **deoxyuridilic acid** to **deoxythymidylic acid.**
- 5-FU incorporated into RNA, interferes with RNA synthesis and causing cytotoxic effect.
- this drug produce anticancer effect in the S – phase of the cell cycle

➢ PK :

- Oral absorption of 5-FU is unreliable & Because of its severe toxicity to the GI tract, primarily used by **i.v.** infusion or, in the case of skin cancer , given **topically**.
- 5-FU rapidly **metabolized** by dihydropyrimidine dehydrogenase **(DPD)** resulting in a plasma T1/2 15- 20 mins after i.v. infusion
- Genetic deficiency of DPD – severe 5-FU toxicity

➢ AE :

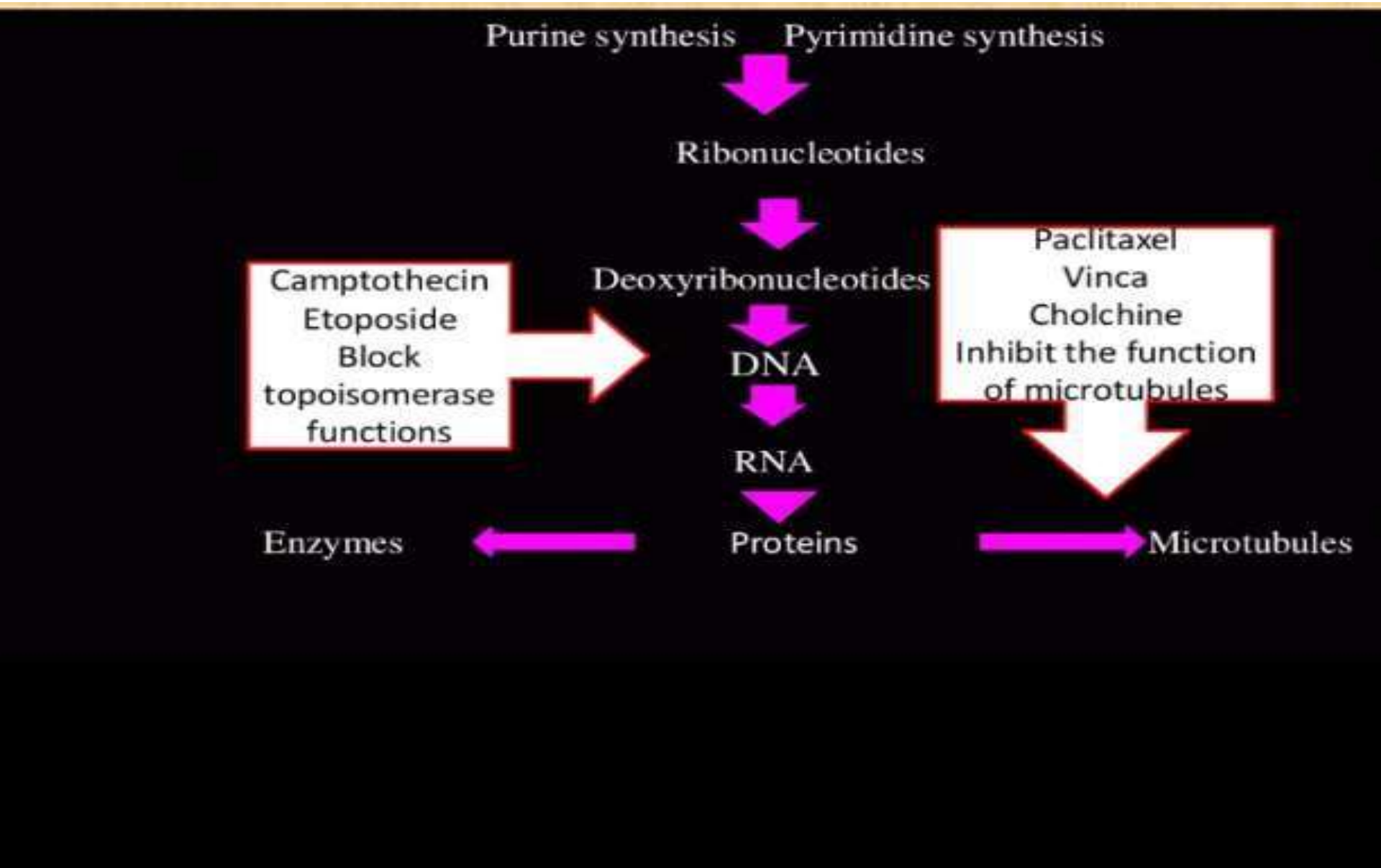
- N/v/d, alopecia, severe ulceration in the oral & GI mucosa, myelosuppression , mucositis, peripheral neuropathy, BMD (with bolus injection), & anorexia are frequently encountered.
- 5-FU also cause " **HAND- FOOT SYNDROME** "is seen after extended infusions.

➢ USED :

- primarily in the treatment of slow growing solid tumors (colorectal, breast, ovarian, pancreatic, & gastric carcinoma)

- **Dose** – 25 mg/m2 BSA daily for 5 days every 28 days by i.v. infusion

Natural products :



A) Vinca Alkaloids : Vincristine & vinblastine

- **MOA : (**mitotic spindle inhibitor)

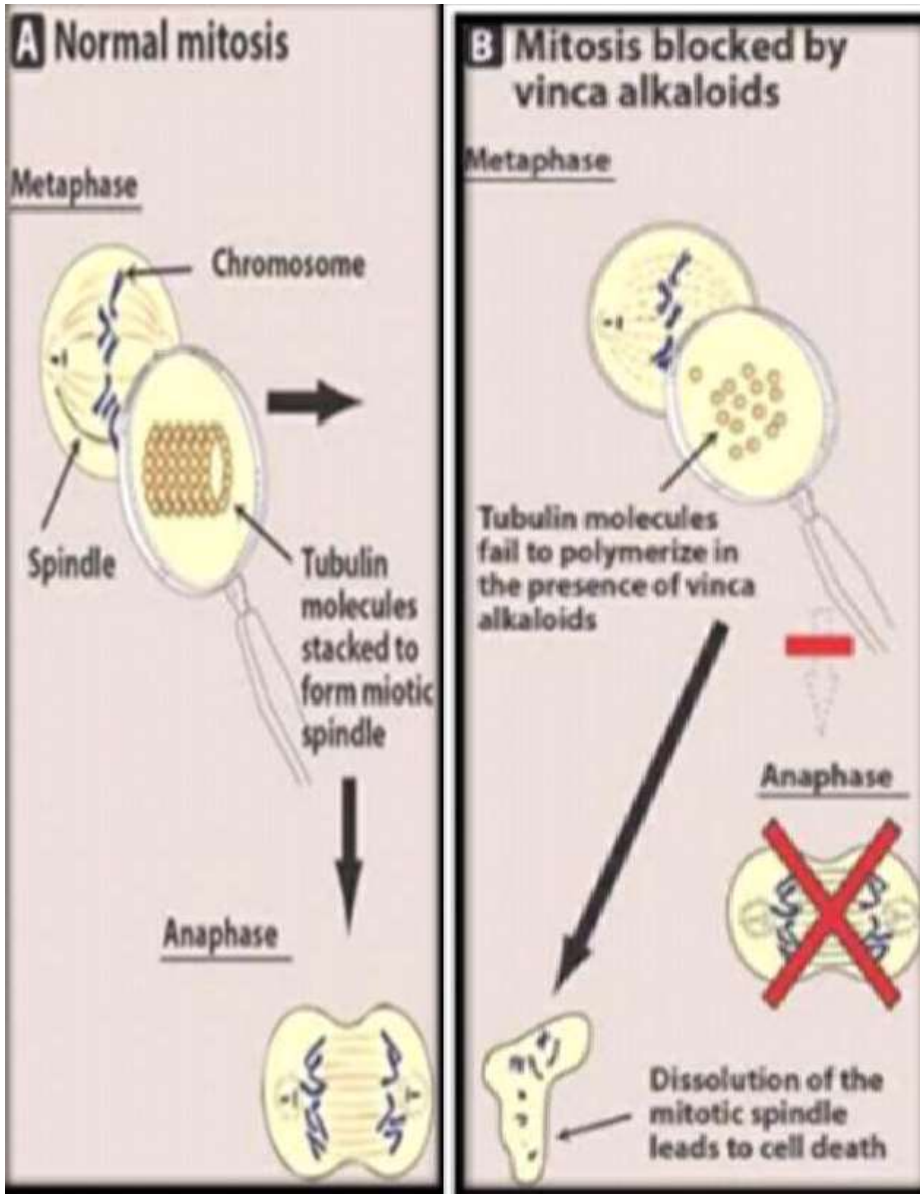
-these agent bine specifically to protein tubulin & **inhibit polymerization of microtubules.**

-This **prevent formation of spindles** & **blockade of mitotic division** at metaphase.

-they act primarily on the **M phase** of cancer cell cycle.

- **PK**- given **parenterally**, penetrate most tissues except CSF cleared mainly via biliary secretions
- **AE** :

- leukopenia, mental depression, loss of sleep, headache, n/v, anorexia, constipation, alopecia, peripheral neuritis



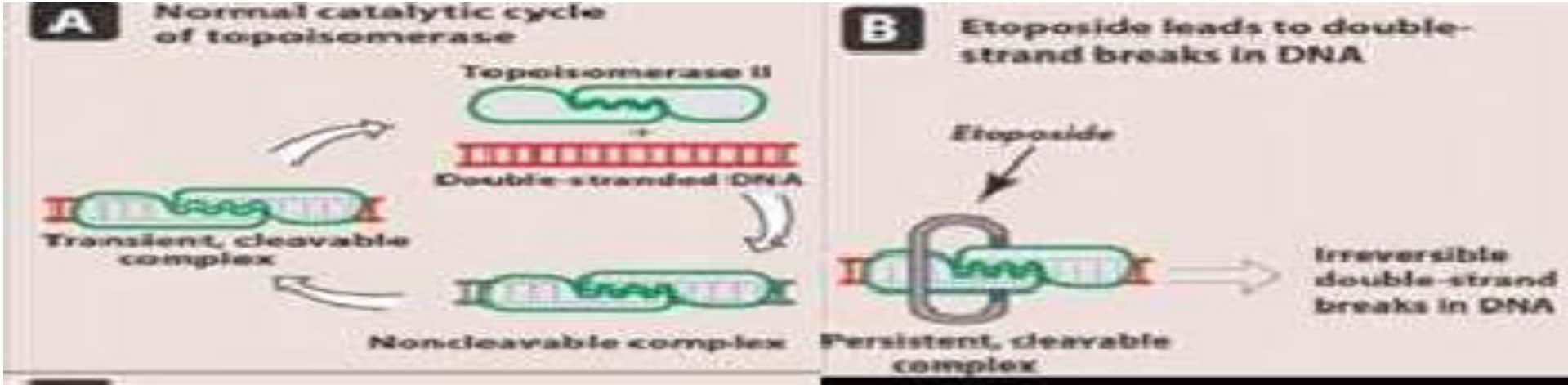
- **Uses :**

- Lymphosarcoma , Hodgkin's disease , lymphatic leukaemia , cancer of breast, testes, kidney

B) Epipodophylotoxin : etoposide,teniposide

- **MOA :**

- They act by inhibition of mitochondrial function & nucleotide transport.
- They also bind to **topoisomerase ||** & DNA, causing breaking of DNA.
- This drug are most active in late s-phase & early G2- phase.

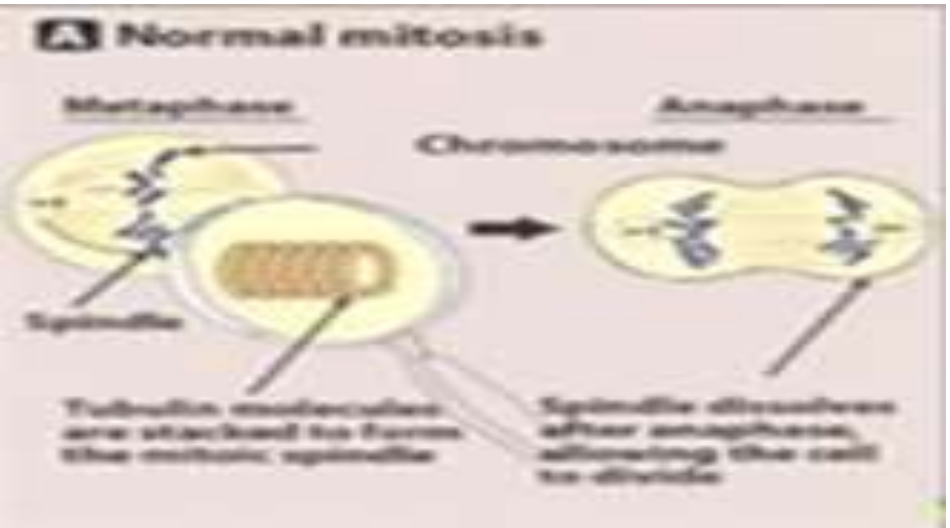


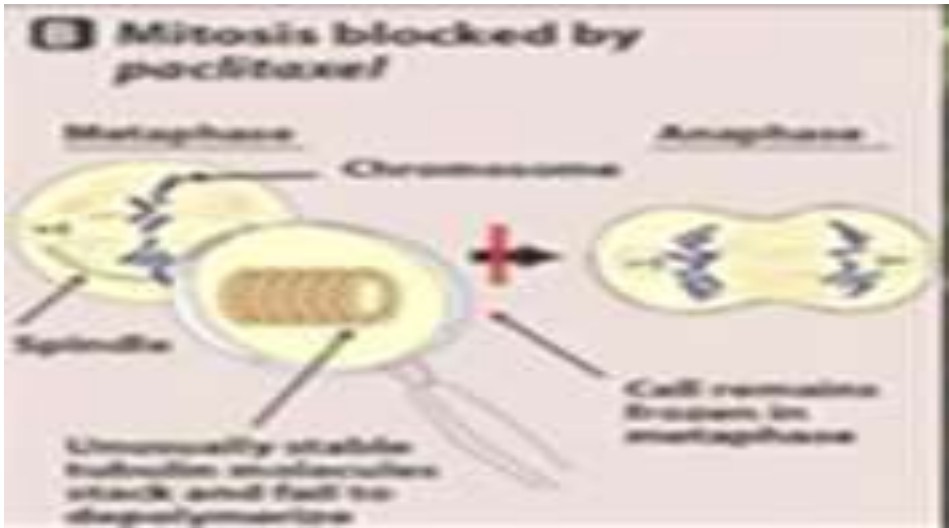
- **PK** : orally well absorbed and distributes to most body tissues , Elimination is mainly via kidneys
- **AE :** n/v , myelosuppression, alopecia
- **USES :** testicular tumor, lung carcinoma along with cisplatin, non-Hodgkin's lymphoma & lymphoblastic leukaemia in children

C) TAXANES : paclitaxel, docetaxel

- **MOA :**

- same as Vinca alkaloid taxans are act on **microtubules** & stabilize them





- **AE :**

- bone marrow depression, alopecia, muscle pain, neurotoxicity
- allergy to paclitaxel is also common and many a time corticosteroids & antihistamines are to be used to control allergy.

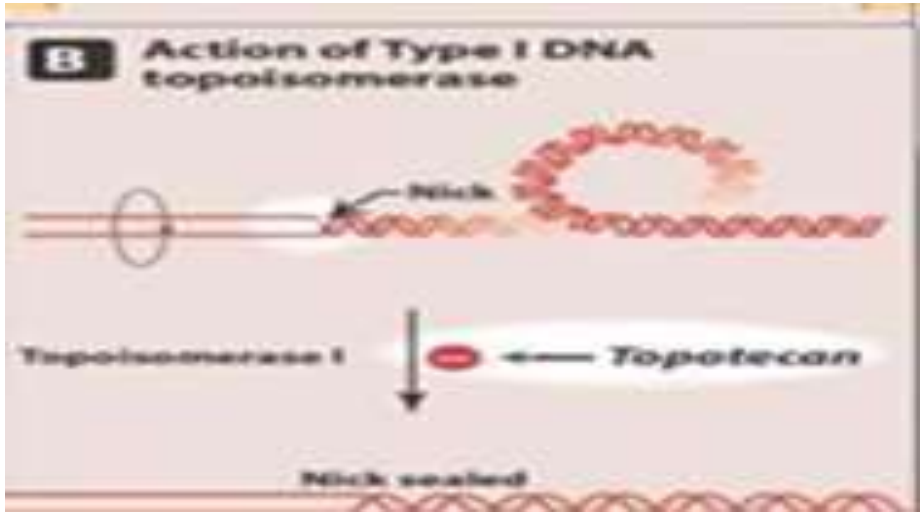
- **USES :**

- ovarian & breast cancer

D) CAMPOTHECINS : Irinotecan , topotecan

- **MOA :**

- they block Topoisomerase-I, which occure in high levels throughout the cell cycle.



- **AE** :

- by campothesin, mild & reversibile AE i.e. Myelosuppression and Diarrhoea

- **PK** :

- Irinotecan – prodrug – converted to active metabolite in liver ,

-Topotecan is eliminated renally, whereas Irinotecan and its metabolite eliminated in bile and faeces

- **USES** :

-Topotecan - 2nd line agent – Advanced Ovarian Cancer and for small cell lung Cancer.

- Irinotecan – Metastatic Colorectal Cancer

Antibiotics :

Actinomycin- D, **Daunorubicin**, Doxorubicin, Mitomycin, **Bleomycin**

1) Actinomycin- D or Dactinomycin :

- **MOA** :It is an anticancer antibiotic which bind with DNA & form complex with it. Also **inhibits topoisomerase ||** & produce cytotoxicity. Also interrupts function of DNA.
- **A.E.** : (Dactinomycin) anorexia, n/v , BMD
- **USES** : in lymphoma, Hodgkin's disease

2) Daunorubicin or Doxorubicin :

- **MOA** :

- it is bind with DNA & **intercalate** with adjacent pairs & disrrupts DNA activity , also **inhibite DNA gyrase** & produce cytotoxicity.

- **PK:**

- Doxo and Daunorubicin must be given IV.
- Metabolized in liver , excreted in bile and urine

- **A.E.** :

- This agents are highly toxic to myocardium & produce arrhythmia, also produce BMD , HT,

- **Uses** :

- Doxorubicin – Hodgkin's and non-Hodgkin’s lymphoma, myelomas, sarcomas, breast, lung, ovarian and thyroid ca.
- Daunorubicin – acute leukemias

3) Bleomycin :

- **MOA** : acts in the G2 phase- generates **free radicals** – bind to DNA – DNA strand breaks – **inhibit DNA synthesis**

- **PK :** Given parenterally, inactivated by tissue amino peptidases mainly

- **A.E.** : that cause minimal BMD but produce serious effect i.e. **pulmonary fibrosis**. rarely produce nausea, vomiting, headache, hypotension
- **cutaneous toxicity** (hyperpigmentation ,hyperkeratosis, erythema and ulcers)
- bleomycin should be given prior to radiation therapy because it's most sensitive to radiation .

- **USES** : used in carcinoma of skin, upper respiratory passages, oral cavity, urinogenital tract.

Enzyme

1) L-Asparaginase :

- Enzyme used for treatment of leukaemia's and lymphomas
- These **tumors require exogenous asparagine** for **growth,**

  L- Asparaginase acts by **depleting this amino acid** in serum.
- Adm. by IV route
- **AE** : hypersensitivity reactions, acute pancreatitis and cortical vein thrombosis

Monoclonal antibodies -

Monoclonal Abs	Targeted against	Indication	Comments
Rituximab	CD-20	Non-hodgkin's lymphoma	
Alemtuzumab	CD-52	Low grade lymphomas and CLL	
Trastuzumab	HER 2/neu	Breast Ca	Can cause cardiotoxicity
Cetuximab and Panitumumab	EGFR	EGFR-positive metastatic colorectal carcinoma	Rash, hypomagnesemia and interstitial lung disease
Bevacizumab	VEGF	Metastatic colorectal ca	Combined with 5-FU

Surgical Resection

- Surgery is the oldest method of treating cancers, with the view to **complete removal** of the cancer **(organ) from the body.**

- Surgery in certain cancers is the most important aspect of the care, and cure may not be possible without it.

- This is true in patients with breast cancer, colon cancer, stomach cancer, non-small cell lung cancer, and many other cancers.

Radiotherapy

- Radiotherapy is treatment with high energy **x-rays** that **target** the **area** of the cancer.
- Cancer cells are more sensitive than normal cells and the **x-rays damage** their **genetic code**. This damage means that they are unable to grow.
- Treatment is designed specifically for each individual.

➢ Why radiotherapy is given?

- After surgery for cancer, there is always a small risk of a few cells remaining in the body. **Radiotherapy** is given to **reduce the chance** of **local recurrence**, i.e. cancer returning in the particular tissue.

- Sometimes radiotherapy is given to treat cancer, when surgery is not an option.
- Ex. : I131 , P32, U198

Planning CT scan

- Before the treatment can start patient will have to come for a planning CT scan. This scan is specifically for designing radiotherapy.
- The scan can take about 30 minutes, in which time you need to lie quite still, but you can breath normally.
- At the end of the planning scan the radiographers will, give you some permanent marks,.

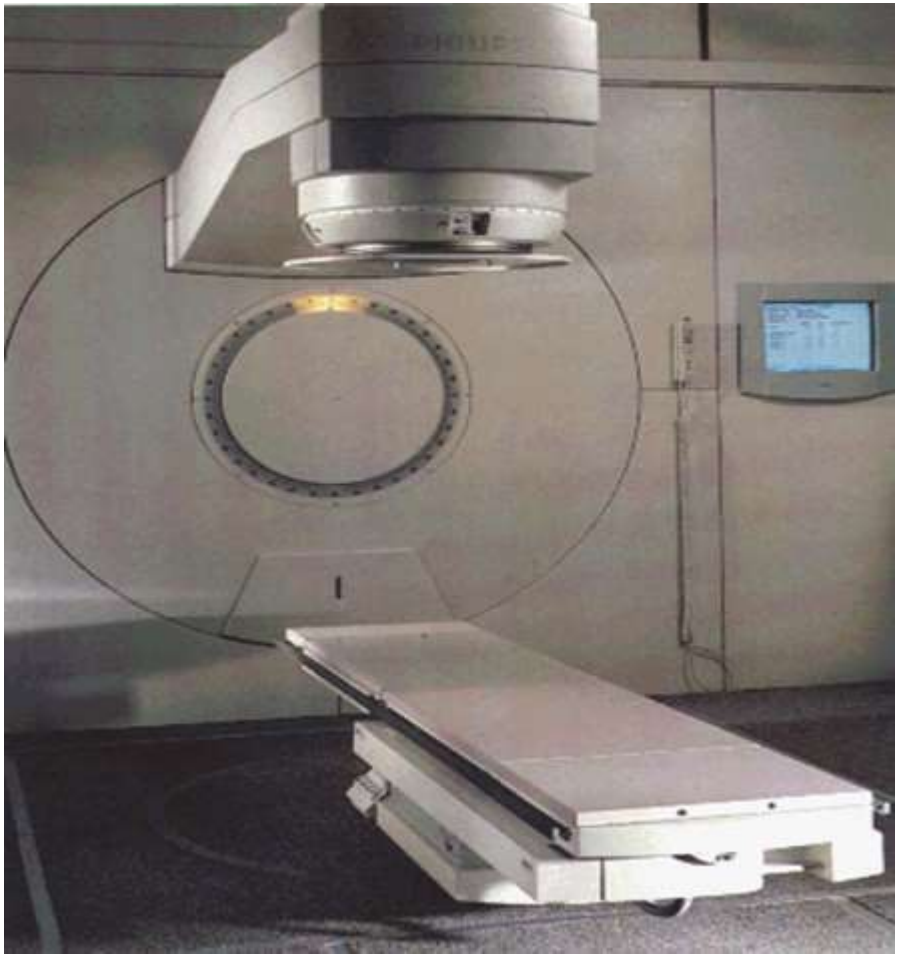
treatment

- The treatment will usually start a few weeks after having planning CT scan. During these weeks consultant and the rest of the planning team will have designed a radiotherapy plan specifically for patient.

- On the day that treatment starts, one of the *treatment radiographers will first discuss the treatment with patient.*

- Patient will be taken into the treatment room and placed in exactly the same position that for the planning scan. The radiographers will set up for the first treatment and then they will leave the room. The radiographers will be watching patient all the time from outside the room on CCTV. After that part of the treatment has been given, the radiographers will return into the room and set up the machine for the next. This process will continue until you have had all the required treatment in each session.

Assembly for the radiotherapy



Immunotherapy

- At the present time the treatment of cancers relies on chemotherapy and radiation both of which have devastating effects on normal non-tumor tissues.
- Because the immune response is highly specific it was long been hoped that tumor specific immunity may be used to selectively eradicate tumors without injuring the patient.
- When cells become cancerous they produce new, unfamiliar antigens. The immune system may recognize these antigens as foreign, and contain or even destroy the cancer cells.

- The main strategies for cancer immunotherapy aim to provide antitumor effectors (antibodies and T cells) to patient actively immunize patient against their tumors and stimulate the patients' own antitumor immune responses

Novel drugs for Cancer

Category	Drug	Mechanism of action	Clinical use	Adverse effects
Protein tyrosine kinase inhibitors	Imatinib	Tyrosine kinases have specific action on tyrosine residues. These are critical components of signal transduction pathways which influence gene transcription and DNA synthesis.	Chronic myelogenous leukaemia, GIT stomal cell tumour	Nausea, vomiting, oedema, muscle cramps, elevation of transaminases, neutropenia, thrombocytopenia
Epidermal growth factor receptor inhibitors	Gefitinib , Eriotinib	Over expression of factor linked to in duction, growth and metastatic potential of non-small cell lung cancer. These drug inhibit this EGFR by binding to tyrosine kinase-ATP binding site.	Metastatic non-small cell lung cancer and other solid tumors	Diarrhoea, skin rashes, anorexia

Category	Drug	Mechanism of action	Clinical use	Adverse effects
Proteosome inhibitors	Bortezomib	Proteosome inhibition prevents degradation of intracellular proteins leading to activation of signalling cascades, cell cycle arrest and apoptosis.	myeloma	Diarrhoea, peripheral neuropathy, bone marrow suppresion, fatigue.
Hormones and antagonists a. Somato-statins analogues	octreotide	It is a longer acting, more potent analogue of somatostatin.	To inhibit secretions of various autocoids from tumor and peptide hormone from carcinoma.	Abdominal pain, nausea, gall bladder stone

Category	Drug	Mechanism of action	Clinical use	Adverse effects
b. Gonado-trophin release hormone (Gn-RH) agonists	Goserelin, buserelin, leuprolide	They inhibit gonadotrophin release and suppress gonadal function due to down-regulation.	Prostatic carcinoma and esrogen receptor positive breast cancer	Hot flushes, osteoporosis, loss of libido
c. Gn-RH antogonists	Cetrorelix, ganirelix, abarelix		Prostate carcinoma	Less toxic than agonists, pain and swelling at the injection site
d. cortico-steroids	Dexa-methasone, prednisolone	Glucocorticoids decrease the release of cytokines from lymphocytes which reduces tissue damage	Lymphocytic leukaemia, hodgkin's disease, multiple myeloma	Susceptibility to infection

Future prospects

- p53 mutated from tumor suppresor gene to an oncogene. Administration of ONYX-015 (an oncolytic virus) lyses the tumor cells without affecting the cells expressing normal p53 protein.
- *Telomerase inhibitors* are now being considered as potential anticancer drugs of future.
- Due to the antigens present on the tumor cells, antibody can be designed to selectively target such tumorous cells.
- Progress through the cell cycle is controlled at check points during the cycle. The check point is controlled by specific kinases (cyclin dependent kinases-CDKs) that are activated by binding to the proteins termed as cyclins. Small molecule inhibitors of CDKs (e.g., favopiridol) are being explored as newer anticancer drugs.